

REVIEW

Immunological functions of liver sinusoidal endothelial cells

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Liver sinusoidal endothelial cells (LSECs) line the liver sinusoids and separate passenger leukocytes in the sinusoidal lumen from hepatocytes. LSECs further act as a platform for adhesion of various liver-resident immune cell populations such as Kupffer cells, innate lymphoid cells or liver dendritic cells. In addition to having an extraordinary scavenger function, LSECs possess potent immune functions, serving as sentinel cells to detect microbial infection through pattern recognition receptor activation and as antigen (cross)-presenting cells. LSECs cross-prime naive CD8 T cells, causing their rapid differentiation into memory T cells that relocate to secondary lymphoid tissues and provide protection when they re-encounter the antigen during microbial infection. Cross-presentation of viral antigens by LSECs derived from infected hepatocytes triggers local activation of effector CD8 T cells and thereby assures hepatic immune surveillance. The immune function of LSECs complements conventional immune-activating mechanisms to accommodate optimal immune surveillance against infectious microorganisms while preserving the integrity of the liver as a metabolic organ. *Cellular & Molecular Immunology* (2016) **13**, 347–353; doi:10.1038/cmi.2016.5; published online 4 April 2016

Keywords: CD8 T cells; cross-presentation; liver; LSEC

HEPATIC MICROANATOMY IS LINKED TO PHYSIOLOGICAL LIVER FUNCTION

The liver serves primarily as an organ with metabolic functions but also exhibits unique immune functions that confer lymphoid tissue-like functionality to the liver.^{1–3} As a consequence of this hierarchical order of physiological functions, immune regulation of the liver follows the principle of “function follows form”, whereas in lymphoid tissues the principle “form follows function” is realized, as lymphoid tissue microarchitecture is optimally suited to induce or regulate immune responses.⁴

The liver’s microarchitecture, however, is primarily designed to allow for optimal function as a metabolic organ, that is, low-pressure blood perfusion together with all hepatocytes being constantly exposed to blood passing through the extensive meshwork of liver sinusoids. Nutrient-enriched venous blood originating from the gastrointestinal tract mixes after extensive ramification of the portal vein in the portal tract within sinusoids, together with arterial blood. This gives rise to a mixed arteriovenous blood perfusion that allows hepatocytes to metabolize nutrients within both the arterial and venous blood. Being highly specialized in metabolic function to generate proteins, lipids and carbohydrates together with elimination of toxic compounds via

bile, hepatocytes require complementary help by other liver cell populations to perform non-metabolic functions. Liver sinusoidal endothelial cells (LSECs) are the most efficient endocytic cell population of the body; they scavenge molecules from the bloodstream^{5–7} and then transport them in a trans-cytotic manner from the sinusoidal lumen to the hepatocyte surface.⁸ By doing so, LSECs assist the metabolic function of hepatocytes by allowing much more efficient extraction of molecules from the blood stream than what is limited by simple diffusion across endothelial fenestrae, which allows for direct access of blood-borne molecules to the space of Disse and hepatocytes. Hepatic stellate cells, as peri-sinusoidal cells, are localized in the space of Disse in between hepatocytes and LSECs.⁹ Hepatic stellate cells span the circumference of the liver sinusoids and control blood perfusion through contraction and reduction of the sinusoidal diameter.¹⁰ Moreover, hepatic stellate cells represent the body’s main store of vitamin A, thereby complementing the metabolic function of hepatocytes. Excretion of bile from hepatocytes occurs through directed transport to the basolateral surface and secretion into bile canaliculi that eventually terminate in bile ducts within the portal venous tracts, which in turn drain into larger bile ducts for delivery into the gallbladder and the gut. It is of interest to note

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Received: 24 November 2015; Revised: 13 January 2016; Accepted: 13 January 2016

that bile flow occurs in the opposite direction as blood flow. Similar to bile flow, lymphatic drainage of the liver is directed from the central vein to the portal tract.¹¹ LSECs serve a dual purpose in not only separating hepatocytes from the blood flow in liver sinusoids but also facilitating lymphatic drainage within the space of Dissé. This second function may explain the close similarity in phenotype, the expression of characteristic surface molecules and the functional properties between LSECs and lymphatic endothelial cells. Finally, liver myeloid cells, collectively termed Kupffer cells, function as a large scavenger cell population localized in the liver sinusoids to phagocytose particles beyond 200 nm, including microbial debris or even gut-derived microbial microorganism that reach the liver within the bloodstream.^{12–14} This scavenger function of myeloid cells serves as a firewall function to the liver for clearance of bacteria from the bloodstream that have escaped elimination by gut-associated myeloid cells.¹⁵

The liver sinusoid functions both in separating the intravascular compartment from hepatocytes and at the same time, serves as a platform for various immune cell populations to lodge in the liver. Thus, specialized natural killer cell populations, innate lymphocytes including so-called MAIT (mucosa-associated invariant T) cells and myeloid cells adhere to the surface of LSECs to achieve liver residency. In particular, expression of the chemokine receptors CXCR6 and CX₃CR1 appear to facilitate such retention of immune cells in the liver sinusoids in combination with expression of CXCL16 and CX₃CL1 by LSECs.¹⁶ As these receptor–ligand interactions are not unique to the liver the question remains whether liver-specific recruitment processes exist.

Under conditions of chronic inflammation, the portal tract area, which is comprised of branches of the portal vein, the hepatic artery and a bile canaliculus together with portal fibroblasts, can enlarge and transform into tertiary lymphoid tissue. The mechanisms determining the enormous plasticity of this unique anatomic compartment of the liver are still largely unclear. Macrovascular endothelial cells in the portal tract, as well as those around the central vein, differ from microvascular LSECs and support the notion that LSECs and hepatocytes coexist in a close symbiotic manner to support the metabolic function of the liver.

SCAVENGER AND SENTINEL FUNCTION OF LSECs

LSECs have the highest endocytic uptake in the body,^{6,17} and also outpace professional antigen-processing immune cell populations such as dendritic cells or myeloid cells, in terms of uptake of circulating antigens.¹⁸ Being equipped with different classes of scavenger receptors, as well as the mannose receptor, LSECs can extract a broad variety of molecules from blood percolating through the liver.^{19,20} Because of the extensive ramification of the blood vessels entering the liver, the perfusion pressure at the level of liver sinusoids is very low, resulting in blood flow below 100 $\mu\text{m/s}$ and low shear pressure.²¹ These conditions facilitate endocytic uptake of blood-borne molecules by LSECs. In addition to their expression of scavenger receptors, LSECs also express numerous pattern recognition receptors. These mainly comprise Toll-like receptors (TLRs) that are localized on the plasma membrane at the cell surface or in the endocytic compartments. The enormous scavenger capacity also explains the high sensitivity for detecting TLR ligands by LSECs, which can respond to very

low concentrations of lipopolysaccharide (<100 pg/ml) with the production of pro-inflammatory mediators such interleukin (IL)-6.²² Because LSECs are continuously exposed to gut-derived bacterial degradation products delivered to the liver through portal venous blood, it is not surprising that LSECs react only to changes in lipopolysaccharide concentrations, with activation and release of pro-inflammatory mediators but remain refractory to tonic activation through continuous exposure to low concentrations of lipopolysaccharide.²³ Taken together, the highly efficient scavenger function combined with the expression of TLRs allows LSECs to function as very sensitive sentinel cells in the instruction of parenchymal hepatocytes to mount the liver's acute phase response. This supports systemic induction of innate immune effector functions by providing increased levels of complement, C-reactive protein (CRP) and other acute phase proteins.

LSEC-released IL-6 is crucial for the induction of the hepatic acute phase response as it triggers hepatocyte activation and release of CRP or other complement factors that help to mount innate immunity against infection throughout the entire body.²⁴ Furthermore, cytokines released by LSECs upon TLR-mediated activation serve as antiviral effectors and contribute to the control of viral infection of hepatocytes.²⁵ Thus, the paracrine mediators released from TLR-stimulated LSECs serve to not only augment innate immunity locally in the liver but also systemically.

Moreover, by virtue of their scavenger activity, LSECs may also contribute to liver targeting of hepatotropic viruses such as hepatitis B virus (HBV) or hepatitis C virus. In an animal model of HBV infection, rapid accumulation of viruses is observed in LSECs, and considering that only one single virus is sufficient to induce productive infection, transcytosis of virus initially ingested by LSECs for subsequent infection of hepatocytes is very likely.^{26,27} Similarly, accumulation of adenoviruses, which also shows prominent hepatotropism, has been reported to occur in LSECs.²⁸ Thus, scavenger activity not only confers many different functions to LSECs in innate immune defense but also to viral infection of the liver.

SILENCING OF T-CELL ACTIVATION BY LSECs

Beyond scavenger receptors, LSECs also express C-type lectin receptors such as L-SIGN and LSECtin.^{29,30} These receptors are involved in the uptake of molecules bearing mannose residues and may thereby contribute to the clearance of pathogens from circulation. The T-cell surface molecule CD44, which is expressed on activated T cells, has been identified as an endogenous ligand for LSECtin. LSECtin binding to CD44 has been demonstrated to occur in a protein-glycan-dependent manner, and this interaction leads to inhibition of T-cell activation, proliferation and effector function, which indicates a key role for LSECtin expression in controlling local T-cell activation and effector function.³¹ Indeed, in the absence of LSECtin *in vivo*, increased T cell-mediated immunity and liver damage was observed. Thus, LSECs directly contribute to inhibition of effector function of activated T cells.

Furthermore, LSECs also prevent the antigen-specific activation of CD8 T cells locally in the liver. T-cell activation by antigen-presenting dendritic cells was prevented if LSECs also had physical contact with T cells. This vetoing function of LSECs on other antigen-presenting cell populations in the liver is most likely

explained through diversion of the critical signaling molecule LFA-1 on T cells away from the antigen-presenting cell to LSECs, thereby depriving the immunological synapse of a key signaling component.³² Because LSECs serve as platform for immune cell populations to adhere in the sinusoids and are therefore in continuous physical contact with all immune cells that arrest there,³³ it is possible that these two veto mechanisms prevent local antigen-specific activation of CD8 T cells and the execution of effector functions. However, the role of these regulatory features of LSECs for hepatic immune surveillance during microbial infection has not been formally addressed.

INDUCTION OF REGULATORY CD4 T CELLS BY LSECs THROUGH MAJOR HISTOCOMPATIBILITY COMPLEX II-RESTRICTED ANTIGEN PRESENTATION

Low levels of major histocompatibility complex (MHC) II molecules are constitutively expressed on LSECs, and this expression can be further increased by exposure to pro-inflammatory cytokines such as tumor necrosis factor (TNF) or interferon gamma.³⁴ Because LSECs express only low levels of cell surface expressed co-stimulatory molecules and fail to express IL-12, which is crucial for induction of cells with effector function, they do not support differentiation of naive CD4 T cells into helper CD4 T cells.³⁵ Instead, the outcome of antigen-specific stimulation of naive CD4 T cells by antigen-presenting LSECs, through transforming growth factor-beta or Notch-dependent signaling mechanisms, is the differentiation into T cells with regulatory potential. Expansion of regulatory T cells is also promoted by LSECs, indicating that this cell population has a crucial role in induction and proliferation of regulatory T cells *in vivo*.³⁶ It is of interest to note that the liver does not contain an excessive amount of regulatory T cells, as identified by the transcription factor Foxp3 and that these cells are rather recruited upon inflammation through similar chemokines that recruit effector T cells.³⁷ However, LSEC-induced regulatory T cells may not necessarily express the transcription factor Foxp3, which may cause an underestimation of the number of regulatory T cells present in the liver.³⁸

Induction of regulatory T cells through LSECs *in vivo* can be achieved through the use of their scavenger function, demonstrating the translational potential for using hepatic immune regulation for immune therapy.³⁹ Linking antigen to nanoparticles leads to its preferential accumulation in LSECs and the induction of regulatory T cells.⁴⁰ Such LSEC-induced regulatory T cells have the capacity to interfere with ongoing immune responses not only in the liver but also in other organs as well. LSEC-induced regulatory T cells can prevent the development of, and even ameliorate, ongoing central nervous system-based autoimmunity.⁴¹ These T cells are also remarkably stable in their functional properties, which appears to be different from regulatory T cells induced by other antigen-presenting cell populations that show eventual reversion to helper T-cell populations.⁴²

LSECs CROSS-PRESENT SOLUBLE ANTIGEN ON MHC I MOLECULES TO CD8 T CELLS

MHC I-restricted antigen presentation primarily displays endogenous proteins processed via proteasomal cleavage to CD8 T cells.

Some cell populations, such as certain dendritic cell populations, myeloid cells and B cells, also have the capacity to present soluble antigens taken up by receptor-mediated endocytosis to CD8 T cells, a process termed cross-presentation.⁴³ LSECs bear the capacity to cross-present endocytosed soluble antigens to CD8 T cells.⁴⁴ Given their enormous scavenging potential they outperform dendritic cells in antigen uptake by a factor of 10–50.¹⁸ The endocytosed antigen is then cross-presented in a proteasome- and transporter associated with antigen processing-dependent manner on MHC I molecules to CD8 T cells. Upon antigen challenge *in vivo*, LSECs cross-present soluble antigen even better than dendritic cells, demonstrating that the endocytic scavenger function is an important component of LSEC immune function. Interestingly, LSECs do not retain antigen taken up *in vivo* for a longer period of time compared with dendritic cells, a finding consistent with the efficient transcytotic transport of endocytosed cargo from LSECs to hepatocytes *in vivo*.¹⁸ Thus, LSECs exhibit dynamic cross-presentation that is distinct from professional antigen-presenting cells, such as dendritic cells, as they only cross-present antigens for a short period of time.

As a consequence of cross-presentation by LSECs, naive CD8 T cells are retained in an antigen-specific manner to the liver sinusoids. As blood flow is slow in liver sinusoids and adhesion of lymphocytes to sinusoidal cells does not depend on selectin-mediated slowing of circulating lymphocytes, the recruitment of antigen-specific CD8 T cells from the circulation appears to be primarily the result of MHC I–T-cell receptor (MHC I–TCR) interaction.³³ Such antigen-specific retention is the first step in a complex cross talk between cross-presenting LSECs and CD8 T cells that leads to mutual activation of both, characterized by increased expression of MHC I and B7H1 on LSECs and PD1 on CD8 T cells.⁴⁵ As a result of co-inhibitory signaling delivered through the B7H1–PD1 axis, CD8 T cells initially activated by cross-presenting LSECs rapidly regain a quiescent state and during this state they are refractory to agonistic antibody-mediated stimulation via either the TCR or phorbol ester-induced activation.⁴⁵ To achieve this quiescent state, the cross talk between LSECs and CD8 T cells must be finely balanced and requires cooperatively tuned signaling through both the TCR and PD1. During this quiescent state, LSEC-activated CD8 T cells fail to show effector functions and do not secrete cytokines, nor display cytotoxic effector functions against tumor cells.^{45,46}

However, scavenger function remains constant over a very wide range of antigen concentrations, leading to a linear increase in cross-presentation of endocytosed antigens to CD8 T cells, thereby increasing signaling through the TCR. In contrast, B7H1 upregulation and consequently PD1 co-inhibitory signaling exhibits a ceiling effect. This results in an unbalance between TCR signaling and PD1 signaling at very high antigen concentrations, typically above 1 mg/ml. In this situation, naive CD8 T cells activated by cross-presenting LSECs differentiate in an IL-2-dependent manner into effector CD8 T cells.⁴⁷ Thus, at very high antigen concentration, such as during infection with hepatotropic viruses such as HBV, cross-presentation by LSECs may induce differentiation of naive CD8 T cells into effector CD8 T cells, thereby directly contributing to pathogen-specific immunity locally in the liver.

LSEC-INDUCED DIFFERENTIATION OF NAIVE CD8 T CELLS INTO MEMORY T CELLS WITH PROLIFERATIVE POTENTIAL

Upon antigen-specific activation through cross-presenting LSECs, naive CD8 T cells undergo modest proliferation and are not clonally eliminated. This argues against induction of deletional tolerance that follows incomplete activation of naive CD8 T cells in the absence of appropriate co-stimulatory signals after TCR signaling. Rather, LSEC-primed CD8 T cells also resist clonal deletion inflicted by immature antigen-presenting dendritic cells, indicating that CD8 T cells primed by cross-presenting LSECs are spared from deletion when antigen is systemically distributed in the absence of inflammation. CD8 T cells activated by cross-presenting LSECs relocate within 24–36 h after their activation in the liver to secondary lymphoid tissues. Within lymph nodes, LSEC-primed CD8 T cells localize to T-cell zones, similar to central memory T cells. Entry into lymphoid tissues is facilitated by rapid T-cell re-expression of CD62L after their initial activation by LSECs and their migration toward the steady-state chemokine CCL19 and CCL21. LSEC-primed CD8 T cells survive even in the absence of antigens for long periods of time, which is consistent with the features of a memory T cell. Importantly, reactivation of LSEC-primed T cells requires simultaneous and combinatorial signaling through the TCR, the co-stimulatory receptor CD28 and the IL-12 receptor.⁴⁸ Thus, LSEC-primed T cells require a fully matured and activated dendritic cell for re-activation, that is, a situation found during microbial infection but not during exposure to auto-antigens. Such re-activation of LSEC-primed T cells is then accompanied by proliferation and later release of effector cytokines, as well as development of cytotoxic effector function.

LSEC-primed CD8 T cells show a distinct transcriptome profile that clearly differentiates them from conventional central memory or effector memory CD8 T cells and from CD8 T cells that are exhausted during chronic viral infection. Whereas memory CD8 T cells generated by professional antigen-presenting cells show upregulation of transcription factors such as Tcf7, Eomes, Bcl6 and Foxo1, and signaling molecules such as Stat3 and Tsc1, LSEC-primed T cells express a much more restricted repertoire of transcription factors consisting of Eomes and Stat3, as well as uniquely upregulated ones such as Zbtb32 and E2F2.⁴⁸

Induction of memory CD8 T cells with proliferative potential in the liver by cross-presenting LSECs does not require inflammation or a functional maturation step by LSECs. Thus, LSEC-induced memory CD8 T-cell differentiation complements conventional memory T-cell formation by fully matured professional antigen-presenting cells (Figure 1). This may be of importance during the common situation where early after infection substantial amounts of viral antigens are released into the circulation without inducing a systemic inflammatory response. Furthermore, many pathogens can subvert innate immunity, and the immune system is then challenged with microbial antigens in the absence of inflammation. During these situations, antigen presentation by immature dendritic cells would clonally eliminate those pathogen-specific T cells that are urgently required to control microbial infection. LSEC-induced memory T-cell differentiation may provide a solution to this problem by preserving the T-cell repertoire necessary to fight infection of these microbes that evade

innate immunity or disseminate their antigens in the systemic circulation, a feature observed after many viral infections.⁴⁹

IL-6 TRANS-SIGNALING AS A CO-STIMULATORY SIGNAL IN MEMORY CD8 T-CELL DIFFERENTIATION BY LSECs

Given the absence of strong co-stimulatory signals, it has been unclear how cross-presentation by LSECs can lead to activation of naive CD8 T cells and initiate differentiation processes that typically depend on co-stimulatory signals delivered through the CD28 or IL-12 receptor. Because isolated signaling through the TCR alone is not sufficient to induce survival and T-cell differentiation, unconventional co-stimulatory molecules are likely used by LSECs. Interestingly, cross-presentation by LSECs to naive CD8 T cells leads to a mutual activation, causing augmented expression of activation markers as well as PD1 on the T-cell side and increased expression levels of MHC I and

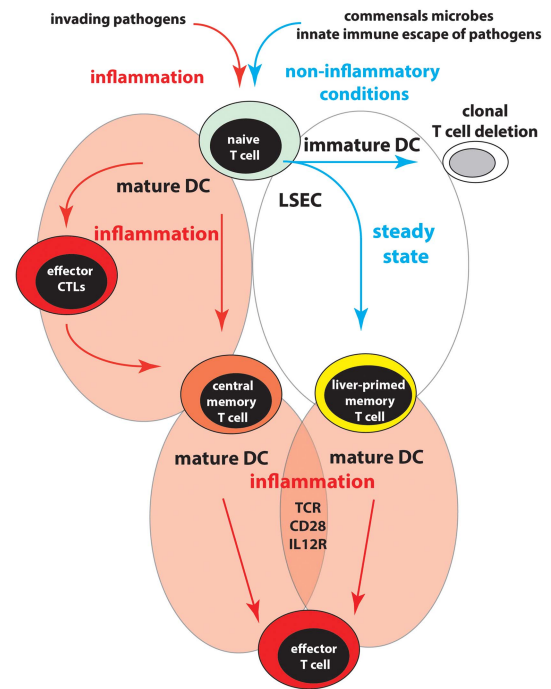


Figure 1 Infection accompanied by inflammation leads to maturation of dendritic cells that will cross-prime naive CD8 T cells and elicit their differentiation into short-lived effector T cells or memory T cells. Upon re-encountering antigen, central memory CD8 T cells are re-activated and through proliferation, will provide sufficient pathogen-specific T-cell progeny to contain infection. In the absence of inflammation, antigens cross-presented by immature dendritic cells will lead to clonal deletion of T cells, thus causing a hole in the TCR repertoire that may affect antiviral immunity because viral antigens often are systemically disseminated during the early phases of infection. Cross-priming by LSECs leads to naive CD8 T-cell activation, which protects these cells from deletional tolerance by immature dendritic cells and causes differentiation into memory T cells with proliferative potential. Upon combinatorial stimulation via the TCR, CD28 and the IL-12 receptor, such LSEC-primed memory T cells are re-activated and start to proliferate and differentiate into effector cells that contribute to elimination of viral and bacterial infections. IL-12, interleukin-12; LSEC, liver sinusoidal endothelial cell; TCR, T-cell receptor.

B7H1, the ligand for PD1, on the LSEC side. This substantiates the notion that cross talk between cross-presenting LSECs and naive CD8 T cells is operating in the context of LSEC-induced T-cell differentiation. The hallmark of rapid differentiation of memory CD8 T cells is the transient acquisition of high granzyme B expression that is associated with temporary cytotoxic function of LSEC-primed T cells. Extensive screening efforts to uncover co-stimulatory mechanisms revealed that blockade of IL-6 released from LSECs during CD8 T-cell cross-priming prevented T-cell activation and differentiation into memory T cells.⁵⁰ Considering that dendritic cells also release IL-6 during T-cell cross-priming but fail to cause rapid granzyme B expression and direct differentiation into memory T cells, a direct effect of IL-6 on T cells is unlikely. The IL-6 receptor is a heterodimeric molecule composed of a ubiquitously expressed gp130 molecule and a second gp80 molecule whose expression is restricted to a few cell populations.⁵¹ IL-6 can couple to gp80 to form a receptor-ligand complex that initiates trans-signaling in gp130-expressing cells that also lack gp80 expression. Such IL-6 trans-signaling provides stronger activation of downstream Stat3 compared with IL-6 binding alone to the endogenously expressed heterodimeric receptor.⁵¹ Cleavage of IL-6 and gp80 provides this strong IL-6 trans-signaling to neighboring cells that lack gp80, such as CD8 T cells. LSECs are unique in providing such IL-6 trans-signaling because they do not release IL-6/gp80 but rather provide this signal in a membrane-bound form in trans. As LSECs establish multifocal immune synapses with CD8 T cells during cross-priming, it is likely that such IL-6 trans-signaling provides a unique co-stimulatory signal. It is of interest to note that Stat3 signaling has been shown to be required for differentiation of memory T cells with proliferative potential. Thus, the combination of TCR signaling, together with strong Stat3 activation through IL-6 trans-signaling, may explain the uniform differentiation of CD8 T cells cross-primed by LSECs into memory T cells.⁵⁰ In contrast, cross-priming by dendritic cells alone under inflammatory conditions induces a broad range of different CD8 T cells such as short-lived effector T cells, effector memory T cells and central memory T cells.^{52,53} The mechanisms determining this distinct regulation of co-stimulatory molecules by LSECs and dendritic cells remain unclear but it most likely relates to their distinct origin from precursor cells in the liver versus the bone marrow.

LSECs FUNCTION IN IMMUNE SURVEILLANCE DURING HEPATOCYTE INFECTION

LSECs not only contribute to the generation of memory CD8 T cells but also directly engage in the local activation of circulating or liver-resident effector CD8 T-cell populations. Hepatocytes do not express high levels of MHC I molecules and are not directly exposed to T cells passing through liver sinusoids. Notwithstanding their passenger status, lymphocytes have been demonstrated to contact hepatocytes while being located in the sinusoidal lumen, by projecting their cellular extensions through endothelial fenestrae.⁵⁴ Virus-specific CD8 T cells have been shown to execute their effector function and kill hepatocytes while still being located within the sinusoidal lumen.⁵⁵ The primary mode of contact for those T cells that directly recognize antigen on infected hepatocytes, that arrest on liver sinusoids and establish contact with

hepatocytes, is mediated in a nonspecific manner by transiently adherent platelets.⁵⁵ LSECs also contribute to hepatic immune surveillance by cross-presentation of viral antigens released from virus-infected hepatocytes. Such cross-presentation of hepatocyte-derived antigens leads to antigen-specific retention in an MHC I-restricted manner and eventually causes stimulation of circulating effector CD8 T cells that are specific for this antigen.³³ Because blood flow in liver sinusoids is slow, there is no need for selectin-induced rolling of lymphocytes before establishment of physical interaction with sinusoidal cells.²¹

Selective antigen presentation by virus-infected hepatocytes *in vivo* using mice with hepatocyte-restricted expression of a particular MHC I molecule elicits only 40–50% of antiviral T-cell immunity and viral hepatitis compared mice with ubiquitous expression of this MHC I molecule. This clearly demonstrates that direct recognition of virus-infected hepatocytes by specific CD8 T cells accounts for only a part of the overall antiviral immune surveillance of the liver. Importantly, selective antigen presentation by LSECs or myeloid cells in the complete absence of MHC I-restricted antigen presentation by virus-infected hepatocytes causes viral hepatitis and hepatic immune surveillance that is comparable to ubiquitous MHC I expression.⁵⁶ Because virus-infected hepatocytes in this model cannot present viral peptides in the context of MHC I molecules, CD8 T cells must be activated by non-hepatocytes that are cross-presenting viral antigens and exert their effector function in an MHC I non-restricted manner. In addition, LSECs are the predominant sinusoidal cell population engaging in cross-presentation of hepatocyte-derived viral antigens to CD8 T cells. Killing of LSECs, however, is not the effector mechanism by which CD8 T cells achieve killing of virus-infected hepatocytes. Instead, CD8 T cells activated by cross-presenting LSECs release TNF that then acts selectively on hepatocytes to induce cell death.⁵⁶ The mechanisms determining this highly selective elimination of virus-infected, but not healthy non-infected hepatocytes, have not been identified to date. However, it is evident that TNF receptor signaling in virus-infected hepatocytes causes caspase activation leading to hepatocyte apoptosis (Figure 2). This LSEC-induced CD8 T-cell activation likely increases immune surveillance against viral infection of the liver even in the presence of a possible viral escape from MHC I-restricted antigen presentation in infected hepatocytes. Hepatic immune surveillance by LSECs may also be ensured by the fact that hepatic stellate cells are able to transfer MHC I molecules to LSECs. This hepatic cross talk between non-parenchymal cells in the liver may be a backup for proper MHC I antigen presentation by LSECs.⁵⁷

CONCLUSION

LSECs represent a highly versatile liver-resident cell population that combines extraordinary scavenger activity together with evolved immune functions such as cross-presentation. LSECs are key regulators of immune responses in the liver because of their strategic location in the liver sinusoid and their huge cumulative surface area for interaction with passenger leukocytes or other liver-resident immune cell populations. Compared with professional antigen-presenting cells, such as dendritic cells, LSECs use unique mechanisms to establish interaction with

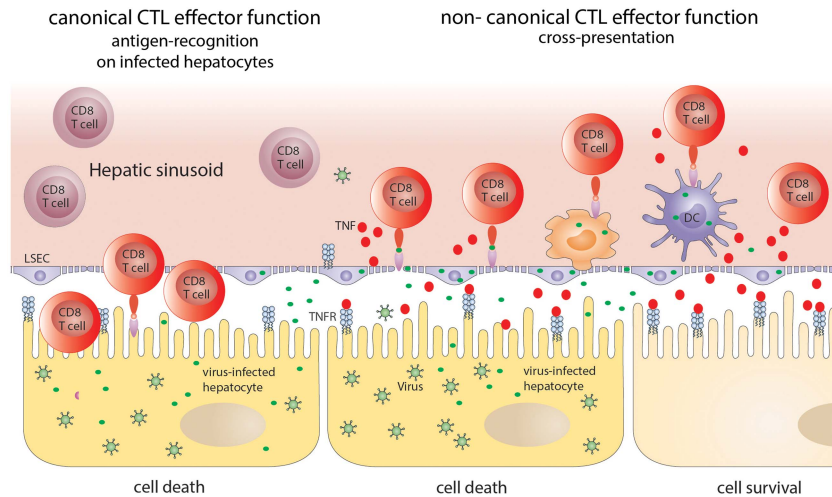


Figure 2 Conventional CD8 T-cell effector function is mediated by recognition of viral peptides presented by infected hepatocytes on MHC I molecules, thus triggering effector cell function and killing by release of perforin and granzyme B. Non-canonical CD8 T-cell effector function is initiated independently from direct recognition of infected target cells by effector CD8 T cells. Rather, cross-presentation of viral antigens released from infected hepatocytes through LSECs leads to activation of effector CD8 T cells. Such activation triggers expression and release of TNF that then acts selectively on virus-infected, but not healthy, hepatocytes to induce caspase-dependent cell death. LSEC, liver sinusoidal endothelial cell; MHC, major histocompatibility complex; TNF, tumor necrosis factor.

passenger lymphocytes, provide instructional programming signals and elicit local effector functions of antigen-specific effector CD8 T cells. Using these particular immune features of LSECs for future immune therapeutic strategies may be useful in overcoming chronic viral infections of the liver.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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